REMARKS/ARGUMENTS

Status of the Claims

Claims 1-3, 7, 10-18, 28-32, and 34-39 are pending in the present application. Claim 8 has been cancelled without prejudice to or disclaimer of the subject matter contained therein. Claims 3 and 7 has been amended to correct errors in antecedent basis. Claims 1, 7, 32, 34-36, and 39 have also been amended as described elsewhere herein. No new matter has been added by amendment. Reconsideration and withdrawal of the rejection is respectfully requested.

The Rejections Under 35 U.S.C. § 112, First Paragraph, Should be Withdrawn

The Examiner has rejected claims 1-3, 7, 8, 10-18, 28-29, 32, and 34-39 under 35 U.S.C. § 112, first paragraph, on the grounds that they lack a sufficient written description. Claim 8 has been cancelled to expedite prosecution, thereby rendering the rejection of this claim moot. It is respectfully submitted that the rejection should not be applied to claims 1-3, 7, 10-18, 28-29, 32, and 34-39 for the reasons described below.

The Examiner states that the specification does not provide support for the ligand binding site "set forth as amino acids 4038-4547 of SEQ ID NO:2" as recited in claims 1(f), 7(f), and 32. Applicants acknowledge the error noted by the Examiner; in fact lines 7-8 of page 35 refer to the Cry1A binding site *encoded* by nucleotides 4038-4547 of SEQ ID NO:1. Claims 1, 7, and 32 have been amended to correct this error, thereby obviating the rejection.

In the Final Office Action mailed May 14, 2004, the Examiner rejected claims 1(f)-3, 7(f), 8, 10-18, and 32 under 35 U.S.C. § 112, first paragraph, on the grounds that polypeptides comprising a fragment of SEQ ID NO:2 as recited in claims are not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time the application was filed. In the advisory action mailed August 5, 2004, the Examiner states that the rejected claims do not meet the written

description requirement because they encompass sequences other than *Ostrinia nubialis* sequences. The rejection is respectfully traversed for the reasons described below.

In the Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description," 66 Fed. Reg. 1099 (Jan. 5, 2001), the USPTO states that the written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant, identifying characteristics, *i.e.* complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of these characteristics." *Id.* at 1106. This standard for the written description requirement set forth in the *Guidelines* was also adopted by the Federal Circuit in *Enzo Biochem, Inc. v. Chugai Pharma U.S.A., Inc.*, 296 F.3d 1316 (Fed. Cir. 2002).

Claims 1-3, 7, 10-18, 28-29, 32, and 34-39 meet the requirements for written description under the *Guidelines* and *Enzo* because they provide the relevant, identifying characteristics, including the partial structure and functional characteristics, of the claimed polypeptides. Claims 1(f), 7(f), and 32 encompass only those polypeptides that contain a ligand binding site having the specified sequence and have *Bt* toxin binding activity. Similarly, claims 1(b)-(e), 7(b)-(e), 28, 29, 34, and 37-90 encompass only those sequences having a designated level of sequence identity with the disclosed *ECB Bt* toxin receptor sequence, where the encoded receptor has *Bt* toxin binding activity. The specification provides guidance regarding the functional domains of the novel ECB *Bt* toxin receptor, including the toxin binding site and the transmembrane domain, in Figure 1 and on lines 5-10 of page 35 The specification also provides examples of assays for *Bt* toxin binding activity on lines 20-29 of page 5.

Accordingly, claims 1-3, 7, 10-18, 28-29, 32, and 34-39 provide the relevant, identifying structural and functional characteristics of the members of each claimed genus of sequences that distinguish them from other sequences. Based on these features, one skilled in the art would be able to determine the identity of the members of the claimed genera of sequences, and would recognize that the Applicants were in possession of the claimed invention.

Applicants note that the claims in this case are analogous to those at issue in the Board of Patent Appeals and Interferences appeals decisions in *Ex Parte Sun*, 2003-1993 (Bd. Pat. App.

Int., Jan. 20, 2004) and *Ex Parte* Vogelstein, 2002-0779 (Bd. Pat. App. Int., Dec. 30, 2002). For the convenience of the Examiner, copies of the Board's decisions in these cases are provided with the present response as Appendices A and B, respectively.

In *Ex parte Sun*, the Examiner had rejected claims directed to sequences having 80% identity with a novel maize protein tyrosine kinase (Wee1) on the grounds that the specification did not provide a sufficient written description or an enabling disclosure for these variants. The Board reversed the Examiner on both rejections, noting that the specification provided the polypeptide and polynucleotide sequence of the novel kinase and provided assays for screening for the activity of the protein. The Board stated that the analysis of the written description and enablement requirements "dovetailed" under these facts, and found that the guidance provided in the specification was sufficient to meet both requirements under U.S.C. § 112, first paragraph.

In *Ex parte Vogelstein*, the Examiner had rejected claims directed to methods that encompassed the use of fragments of the human p53 tumor suppressor gene on the grounds that it would require undue experimentation to generate functional fragments. The Board reversed this rejection, noting that the specification provided guidance regarding domains required for p53 function and methods for identifying functional p53 variants. Based on this guidance, the Board concluded that no undue experimentation would be required to make and test a series of deletion mutants of p53, and the claimed method met the requirements of U.S.C. § 112, first paragraph.

The present case meets the requirements of 35 U.S.C. § 112, first paragraph, as set forth by the Board in *Ex parte Sun* and *Ex parte Vogelstein*. The specification of the present application provides the nucleotide sequence and polypeptide sequence of the novel *ECB Bt* toxin receptor, guidance regarding the receptor's functional domains, and assays for receptor activity. In addition, claims 1-3, 7, 10-18, 28-29, 32, and 34-39 provide the relevant structural and functional characteristics which identify the claimed genera of fragments and variants. Accordingly, these claims meet the requirement for written description under 35 U.S.C. § 112, first paragraph.

In addition, the Applicants submit herewith a declaration showing experiments demonstrating that the novel *ECB Bt* toxin receptor is sensitive to Cry1A(b) toxin, and that the

ligand binding site identified on lines 7-8 of page 35 of the specification is required for Cry1A(b) sensitivity. As described in the declaration, bacmid expression constructs containing full length and truncated coding sequences for the *ECB Bt* toxin receptor were transfected into SF9 cells and then assayed for their ability to confer sensitivity to Cry1A(b) toxin. As shown in Table 2 of the declaration, receptors that did not contain the toxin binding site (*i.e.* the truncated receptor encoded by Construct 5) did not show sensitivity to Cry1A(b). In contrast, receptors having deletions only in the cytoplasmic domain (*i.e.* the truncated receptor encoded by Construct 7) retained Cry1A(b) sensitivity. These experiments demonstrate that functional variants of the *ECB Bt* toxin receptor can be identified by following the guidance provided in the specification. Therefore, one skilled in the art would recognize that the Applicants possessed the claimed genera of fragments at the time the present application was filed.

In view of the above amendments and remarks, all grounds for rejection under 35 U.S.C. § 112, first paragraph, have been obviated or overcome. Accordingly, reconsideration and withdrawal of the rejections are respectfully requested.

The Rejection Under 35 U.S.C. 112, Second Paragraph, Should be Withdrawn

The rejection of claims 7, 8, and 33-36 under 35 U.S.C. § 112, second paragraph, on the grounds that they are indefinite for reciting "at least one polypeptide of interest" has been maintained in the Office Action mailed May 14, 2004. Claim 33 has previously been cancelled, and claim 8 is cancelled in the present amendment, rendering the rejection of these claims moot. The rejection of claims 7 and 34-36 is respectfully traversed for the reasons described below.

According to the *Manual of Patent Examining Procedure*, the test for the definiteness of a patent claim is "whether 'those skilled in the art would understand what is claimed when the claim is read in light of the specification.'" *Manual of Patent Examining Procedure* § 2173.02 (8th ed. Revision No. 1 Feb. 2003), citing *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 1 USPQ2d 1081, 1088 (Fed. Cir. 1986). The phrase "polypeptide of interest" as used in claims 7, 8, and 34-36 meets this standard because its meaning would be clear to those of skill in the art when red in light of the supporting specification. The specification states that a fusion

polypeptide can be made with the novel receptor of the invention and one or more polypeptides of interest. The specification further provides rationales for selecting a polypeptide of interest for use in a receptor fusion polypeptide. For example, the specification states that a polypeptide of interest may be used to facilitate purification of the novel receptor protein, to provide for secretion of the novel receptor protein, or to alter the membrane localization and/or topology of the novel receptor protein. The specification also provides examples of polypeptides of interest that may be selected to create fusion proteins having the desired properties (see, for example, pages 21-22 of the specification).

Thus, one of skill in the art, reading claims 7 and 34-36 in light of this supporting description, would be able to ascertain that the polypeptide of interest recited in these claims is a polypeptide that could be fused to the novel receptor sequences of the invention to convey a desired property to the fusion polypeptide. There are numerous examples of such polypeptides of interest in the prior art and such polypeptides are well known to those of ordinary skill in the art. Furthermore, the claims recite only those fusion polypeptides that contain a novel receptor sequence of the invention. Therefore, the metes and bounds of the claim would be readily ascertainable by one of skill in the art.

Nevertheless, the phrase "polypeptide of interest" has been deleted from claims 7 and 34-36. These amendments are made without prejudice solely to expedite prosecution, and the deleted subject matter will be pursued in a continuation application.

In view of the above arguments and amendments, all grounds for the rejection under 35 U.S.C. § 112, second paragraph, have been overcome. Reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSIONS

It is believed that all the rejections have been obviated or overcome and the claims are in condition for allowance. Early notice to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned agent.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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Nora C. Martinez

Nora C. Martinez

Paper No. 27

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte YUEJIN SUN, BRIAN R. DILKES, BRIAN A. LARKINS, KEITH S. LOWE, WILLIAM J. GORDON-KAMM and RICARDO A. DANTE

Appeal No. 2003-1993
Application No. 09/470,526

ON BRIEF

Before WILLIAM F. SMITH, MILLS and GRIMES, Administrative Patent Judges.

MILLS, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. §134 from the examiner's final rejection of claims 2-11, 31, 33 and 35-36 which are the claims on appeal in this application. Claims 14, 32 and 37 have been allowed.

Claim 31 is illustrative of the claims on appeal and reads as follows:

31. An isolated wee1 nucleic acid comprising a member selected from the group consisting of:
(a) a polynucleotide that encodes a polypeptide of SEQ ID NO:2.;
(b) a wee1 polynucleotide having at least 80% identity to the entire coding region of SEQ ID NO:1;

(c) a polynucleotide comprising the coding sequence set forth in SEQ ID NO:1; and
(d) a polynucleotide complementary to a polynucleotide of (a) through (c).

The prior art references relied upon by the examiner are:

Aligue et al. (Aligue), "Regulation of *Schizosaccharomyces pombe* Wee1 Tyrosine Kinase," J. Biol. Chem., Vol. 272, pp. 13320-13325 (1997)

Hemerly et al. (Hemerly), "Dominant negative mutants of the Cdc2 kinase uncouple cell division from iterative plant development," The EMBO Journal, Vol. 14, pp. 3925-3936 (1995)

Grounds of Rejection

Claims 2-11, 31, 33 and 35-36 stand rejected under 35 U.S.C. § 112, first paragraph as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art at the time the application was filed that the inventor had possession of the claimed invention.

Claims 2-11, 31, 33 and 35-36 stand rejected under 35 U.S.C. § 112, first paragraph for lack of enablement.

These rejections are reversed.

DISCUSSION

In reaching our decision in this appeal, we have given consideration to the appellants' specification and claims, to the applied references, and to the respective positions articulated by the appellants and the examiner.

Rather than reiterate the conflicting viewpoints advanced by the examiner and the appellants regarding the noted rejections, we make reference to the examiner's Answer for the examiner's reasoning in support of the rejection, and to the appellants' Brief for the appellants' arguments thereagainst. As a consequence of our review, we make the determinations which follow.

Background

The subject matter of the present application is generally directed to corn plant nucleic acids and their encoded proteins which are involved in cell cycle regulation. Specification, page 4. In particular, the claimed invention is directed to a wee1 homologue from maize, zmwee1, whose activity resembles related protein tyrosine kinases. Specification, page 6. The zmwee1 protein is indicated in the specification to be useful in the genetic engineering of the corn plant to increase maize productivity. Specification, page 3.

More specifically, claim 31 is directed to an isolated wee1 nucleic acid comprising a member selected from the group consisting of: a polynucleotide that encodes a polypeptide of SEQ ID NO:2.; a wee1 polynucleotide having at least 80% identity to the entire coding region of SEQ ID NO:1; a polynucleotide comprising the

coding sequence set forth in SEQ ID NO:1; and a polynucleotide complementary to a polynucleotide described above.

According to the prior art, Aligue, Wee1 tyrosine kinase regulates mitosis by carrying out the inhibitory tyrosine 15 phosphorylation of Cdc2 M-phase inducing kinase. Abstract. The specification confirms this, stating "induced wee1 overexpression results in phosphorylation of p34 at tyrosine-15 (inactivating p34), effectively blocking the transition from G2 into mitosis." Specification, page 37. The "encoded [wee1] protein is an important part of the checkpoint control machinery that regulates $p34^{cdc2}$ activity and it's [sic] participation in the active MPF (maturation promoting factor) complex." Specification, page 36. Wee1 activity can be stimulated by the CDK2-cyclin A complex, or inhibited by nim1. Specification, page 36.

Description

Claims 2-11, 31, 33 and 35-36 stand rejected under 35 U.S.C. § 112, first paragraph as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art at the time the application was filed that the inventor had possession of the claimed invention.

The Federal Circuit has discussed the application of the written description requirement of the first paragraph of § 112 to inventions in the field of biotechnology. See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). The court explained that

> In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus . . . [H]owever, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id.

The Lilly court also stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. at 1567, 43 USPQ2d at 1405. Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id. at 1568, 43 USPQ2d at 1406.

The Federal Circuit has also addressed the written description requirement in the context of DNA-related inventions. See Enzo Biochem, Inc. v. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by 'showing that an invention is complete by disclosure of **sufficiently detailed, relevant identifying characteristics** . . . i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.'" [Emphasis added] Id. at 1324, 63 USPQ2d at 1613 .

The court in Enzo adopted its standard from the USPTO's Written Description Examination Guidelines. See 296 F.3d at 1324, 63 USPQ2d at 1613 (citing the Guidelines). The Guidelines apply to proteins as well as DNAs.

Finally, it is well-settled that the written description requirement of 35 U.S.C. § 112, first paragraph, can be satisfied without express or explicit disclosure of a later-claimed invention. See, e.g., In re Herschler, 591 F.2d 693, 700, 200 USPQ 711, 717 (CCPA 1979): "The claimed subject matter need not be described in haec verba to satisfy the description requirement. It is not necessary that the application describe the claim limitations exactly, but only so clearly that one having ordinary skill in the pertinent art would recognize from the disclosure that appellants invented processes including

those limitations." (citations omitted). See also Purdue Pharma L.P. v. Faulding, Inc., 230 F.3d 1320, 1323, 56 USPQ2d 1481, 1483 (Fed. Cir. 2000) ("In order to satisfy the written description requirement, the disclosure as originally filed does not have to provide in haec verba support for the claimed subject matter at issue.").

We apply the relevant law above to the facts before us. In the present case, the examiner argues that the "specification does not set forth what specific structural or physical features define the claimed isolated nucleic acids and transgenic cells, plants and seeds." Answer, page 4. The examiner argues that one skilled in the art "could not predict the structure and function of isolated nucleic acids comprising a wee1 polynucleotide having at least 80% identity to the entire coding region of SEQ ID NO:1 or a polynucleotide complementary thereto, or cells, plants and seeds transformed therewith. The physical features of the claimed isolated nucleic acids and transgenic cells, plants, and seeds cannot be ascertained in the absence of information about the functional activities of these nucleic acids. Additionally, the specification does not disclose the effect of incorporating the claimed isolated nucleic acids into the genome of a cell or plant." Id.

We find the examiner's argument that one skilled in the art could not predict the structure and function of isolated nucleic acids comprising a wee1 to be confusing in the context of a written description rejection, as predictability is not the legal standard or test for such rejections. However, as best we can understand the examiner's argument, the examiner appears to argue that the specification does not describe a wee1

polynucleotide having at least 80% identity to the entire coding region of SEQ ID NO:1.

The examiner argues that "Applicant's [sic] own specification fails to teach a single representative species with 80% identity and WEE1 function." Answer, page 5.

We do not agree with the examiner that claim 31 lacks written description in the specification and that appellants were not in possession of the claimed invention at the time the application was filed. First, to satisfy the written description requirement it is not necessary that the application describe the claim limitations exactly, but only so clearly that one having ordinary skill in the pertinent art would recognize from the disclosure that appellants invented the claimed subject matter. Thus, we do not find the fact that the specification does not specifically teach the structure of a species with 80% identity and WEE1 function to be dispositive of the written description issue here.

The Enzo court stated that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.'" Id. at 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The specification specifically describes the chemical structures of a polynucleotide that encodes a polypeptide of SEQ ID NO:2 and a polynucleotide comprising the coding sequence set forth in SEQ ID NO:1. The specification also provides an example of how to screen for WEE1 activity, specification, Example 1, pages 33-34 and Example 3. Contrary to the examiner's position, it would reasonably appear that such a description in the specification would constitute sufficiently detailed, relevant identifying characteristics of the claimed subject matter consistent with Enzo (*supra*).

In our view, the examiner has failed to indicate why one of ordinary skill in the art, who is in possession of the very specific chemical structures of a polynucleotide that encodes a polypeptide of SEQ ID NO:2 and a polynucleotide comprising the coding sequence set forth in SEQ ID NO:1, would be unable to recognize, upon reading the disclosure, that appellants invented the claimed subject matter, including homologues sharing structural features with the specifically claimed and disclosed structures.

The examiner relies on Aligue for the teaching that amino acids 363-408 of the 550 amino acid N-terminal regulatory domain of *S. pombe* WEE1 are critical to the function of the regulatory domain. The examiner concludes that because "the functional properties of WEE1 and other proteins reside in specific amino acid residues, changes in these residues could have an effect on WEE1 function." Answer, page 5.

We agree with appellants that the examiner has not established with a preponderance of the evidence, that the combination of the disclosure of the specific chemical structures of a polynucleotide comprising the coding sequence set forth in SEQ ID NO:1, as well as teachings in the specification on how to test for wee1 activity and teachings of the areas of the wee1 gene that can be altered without disturbing substrate recognition are insufficient to describe a wee1 polynucleotide having at least 80% identity to the entire coding region of SEQ ID NO:1. What is evident from the record is those of ordinary skill in the art were aware that most of the variations in amino acid sequences of WEE1 are in the amino terminus, while the carboxy end of the genes are relatively conserved. Those of skill in the art were also aware that the carboxyl terminus and the central portion of the WEE1 protein from *S. pombe* contain the protein kinase domains and sequence crucial for substrate recognition and catalysis. Thus, those of ordinary skill in the art would have recognized from reading the disclosure that the inventors had invented the isolated wee1 having the specific nucleotide and amino acid sequences and variations of these sequences with mutations in described specific areas of Wee1, while avoiding the introduction of mutations in other regions. This teaching, coupled with the ability to test for functional mutants with the assays provided for in the specification, supports appellants' position that the inventors sufficiently described and were in possession of the invention as claimed, at the time of filing of the patent application.

In our view the examiner has not provided sufficient evidence or analysis to indicate why one of ordinary skill in the art having read the disclosure, would not have been able to recognize that the inventors invented the subject matter within the scope of the claims. The rejection of the claims for lack of written description is reversed.

Enablement

Claims 2-11, 31, 33 and 35-36 stand rejected under 35 U.S.C. § 112, first paragraph for lack of enablement.

It is the examiner's position that the specification is enabling for an isolated wee1 nucleic acid comprising a polynucleotide encoding SEQ ID NO:2 and a polynucleotide comprising SEQ ID NO:1, but does not reasonably provide enablement for a wee1 polynucleotide having 80% identity to the coding region of SEQ ID NO:1. Answer, page 6.

Enablement is a legal determination of whether a patent enables one skilled in the art to make and use the claimed invention, Raytheon Co. v. Roper Corp., 724 F.2d 951, 960, 220 USPQ 592, 599 (Fed. Cir. 1983), and is not precluded even if some experimentation is necessary, although the amount of experimentation needed must not be unduly extensive. Atlas Powder Co. v. E.I. Du Pont De Nemours & Co., 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984); W.L. Gore and Associates v. Garlock, Inc., 721 F.2d 1540, 1556, 220 USPQ 303, 315 (Fed. Cir. 1983). Nothing more than objective enablement is required, and therefore it is irrelevant

whether this teaching is provided through broad terminology or illustrative examples. In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971).

An analysis of whether the claims under appeal are supported by an enabling disclosure requires a determination of whether that disclosure contained sufficient information regarding the subject matter of the appealed claims as to enable one skilled in the pertinent art to make and use the claimed invention. In order to establish a prima facie case of lack of enablement, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. See In re Wright, 999 F.2d 1557, 1561-62, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). See also In re Morehouse, 545 F.2d 162, 192 USPQ 29 (CCPA 1976).

The threshold step in resolving this issue is to determine whether the examiner has met his burden of proof by advancing acceptable reasoning inconsistent with enablement. "Factors to be considered by the examiner in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman, [230 USPQ 546, 547 (Bd Pat App Int 1986)]. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." (footnote

omitted). In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404, (Fed. Cir. 1988).

In the present case the examiner provided an analysis of several of the relevant enablement factors on pages 5-9 of the Answer. One of the examiner's primary arguments is that the specification does not disclose any specific structural or functional characteristics of any isolated nucleic acid comprising a polynucleotide having at least 80% identity to the entire coding region of SEQ ID NO:1. Answer, page 7. The examiner also argues that the "specification does not disclose any examples of how to make a transgenic host cell or plant comprising an isolated nucleic acid comprising a polynucleotide having at least 80% identity to the entire coding region of SEQ ID NO:1" or provide "any definitive evidence that introducing any isolated nucleic acid comprising a polynucleotide having at least 80% identity to the entire coding region of SEQ ID NO:1 into a plant will result in an alteration of the plant's phenotype." Id.

The examiner relies on Hemerly to support the position that the transformation of plant material is unpredictable in view of the disclosure. According to the examiner, Hemerly teaches "the transformation of *Arabidopsis* and tobacco plants with isolated nucleic acids encoding wild-type and mutant Cdc2a cell cycle regulatory proteins". Answer, page 8. Transformation of *Arabidopsis* with wild-type Cdc2a and with a Cdc2a mutant designed to accelerate the cell cycle unexpectedly did not affect the development of transgenic plants. The transformation of *Arabidopsis* and tobacco with a Cdc2a mutant designed to arrest the cell cycle did affect the development of transgenic plants as expected. Id.

The examiner concludes (Id., pages 8-9)

> Given the unpredictability of determining the function of isolated nucleic acids comprising a polynucleotide having at least 80% identity to the entire coding region of SEQ ID NO:1, the unpredictability of altering the phenotype of a plant by transforming it with an isolated nucleic acid of SEQ ID NO:1 or isolated nucleic acids comprising a polynucleotide having at least 80% identity to the entire coding region of SEQ ID NO:1, the absence of guidance in the specification for making and using said nucleic acids and transgenic host cells, plants, and seeds, the lack of working examples, and given the breadth of the claims which encompass multiple polynucleotides having at least 80% identity to the entire coding region of SEQ ID NO:1, it would require undue experimentation by one skilled in the art to make and/or use the claimed invention.

Analysis of the enablement requirement in the present case dovetails with our analysis with respect to the written description requirement. In particular, the specification specifically describes the chemical structures of a polynucleotide that encodes a polypeptide of SEQ ID NO:2 and a polynucleotide comprising the coding sequence set forth in SEQ ID NO:1. The specification also provides an example of how to screen for WEE1 activity, specification, Example 1, pages 33-34 and Example 3. Brief, page 9. In addition, the specification page 3, lines 17-31, "describes the level of skill in the art as well as indicating areas of the wee1 gene that can be altered without disturbing substrate recognition." Brief, page 7. Moreover, the specification, page 3, states, "Most of the variations in amino acid sequences of WEE1 are in the amino terminus, while the carboxy end of the genes are relatively conserved. The carboxyl terminus and the central portion of the WEE1 protein from *S. pombe* contain the protein kinase domains and sequence crucial for substrate recognition and catalysis."

We agree with appellants that the examiner has not established that the combination of the disclosure of the specific chemical structures of a polynucleotide comprising the coding sequence set forth in SEQ ID NO:1, as well as teachings in the specification on how to test for wee1 activity and teachings of the areas of the wee1 gene that can be altered without disturbing substrate recognition are insufficient to enable a wee1 polynucleotide having at least 80% identity to the entire coding region of SEQ ID NO:1.

Nor has the examiner established that one of ordinary skill in the art having the chemical structures of a polynucleotide comprising the coding sequence set forth in SEQ ID NO:1 and the ability to test for expression as described in the specification, would be insufficient to transform cells, plants and seeds in view of the success described in the specification. While the examiner relies on Hemerly for the transformation of *Arabidopsis* with wild-type Cdc2a and with a Cdc2a mutant, the examiner has not explained how or why potential unpredictability associated with Cdc2a expression is related to or affects Wee1 expression. Nor is it clear from the examiner's analysis that the examiner has fully considered the state of the art as it relates to the transformation of vectors, seeds and plant cells, as outlined in the specification.

The Patent and Trademark Office Board of Appeals stated:

> The test [for enablement] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed.

Ex parte Jackson, 217 USPQ 804, 807 (1982).

In our view, upon reading the disclosure, those of ordinary skill in the art would have been provided a reasonable amount of guidance to make and use a wee1 polynucleotide having at least 80% identity to the entire coding region of SEQ ID NO:1. The specification, pages 27-29 outlines methods for transfection and transformation of cells and the introduction of DNA into plants. The examples of the specification indicate successful expression of zmwee1 in E. coli as evidenced by the successful inhibition of cyclin-dependent protein kinase. Specification, pages 33-34. In view of the successful transformation of cells with the disclosed and claimed specific wee1, we find no evidence or sufficient indicated reason of record why one of ordinary skill in the art would not have had a reasonable expectation of success in transforming cells and plant cells with a wee1 polynucleotide having at least 80% identity to the entire coding region of SEQ ID NO:1 without undue experimentation.

The rejection of the claims for lack of enablement is reversed.

CONCLUSION

The rejection of claims 2-11, 31, 33 and 35-36 under 35 U.S.C. § 112, first paragraph as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art at the time the application was filed that the inventor had possession of the claimed invention is reversed.

The rejection of claims 2-11, 31, 33 and 35-36 under 35 U.S.C. § 112, first paragraph for lack of enablement is reversed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

REVERSED

WILLIAM F. SMITH Administrative Patent Judge	)	
DEMETRA J. MILLS Administrative Patent Judge	)	APPEALS AND
ERIC GRIMES Administrative Patent Judge	)	INTERFERENCES

Appeal No. 2003-1993
Application No. 09/470,526

PIONEER HI-BRED INTERNATIONAL, INC.
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Paper No. 24

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte BERT VOGELSTEIN,
SUZANNE BAKER,
ERIC R. FEARON, and
JANICE M. NIGRO

Appeal No. 2002-0779
Application No. 08/825,746

HEARD: November 19, 2002

Before WILLIAM F. SMITH, MILLS, and GRIMES, Administrative Patent Judges.

GRIMES, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 4 and 12, all of the claims in the application. Claims 4 and 12 read as follows:

4. A method of supplying wild-type p53 gene function to a cell which has lost said gene function by virtue of a mutation in a p53 gene, comprising:

   introducing a portion of a human wild-type p53 gene into a human cell which has lost said gene function such that said portion is expressed in the cell, said portion encoding a part of human wild-

type p53 protein which is required for non-neoplastic growth of said cell, whereby wild-type p53 gene function is supplied to the cell.

12. The method of claim 4 wherein said portion corresponds to a region of the p53 gene in the cell which contains the mutations.

The examiner relies on the following references:

Frömmel et al. (Frömmel), "An estimate on the effect of point mutation and natural selection on the rate of amino acid replacement in proteins," J Mol. Evol., Vol. 21, pp. 233-257 (1985)

Bowie et al. (Bowie), "Deciphering the message in protein sequences: Tolerance to amino acid substitutions," Science, Vol. 247, pp. 1306-1310 (1990)

Hollstein et al. (Hollstein), "p53 Mutations in human cancers," Science, Vol. 253, pp. 49-53 (1991)

Ngo et al. (Ngo), "Computational complexity, protein structure prediction, and the levinthal paradox," Birkhäuser Boston, pp. 490-495 (1994)

Hodgson, "Advances in vector systems for gene therapy," Exp. Opin. Ther. Patents, Vol. 5, No. 5, pp. 459-468 (1995)

Verma et al. (Verma), "Gene therapy – promises, problems and prospects," Nature, Vol. 389, pp. 239-242 (1997)

Anderson, "Human gene therapy," Nature, Vol. 392, pp. 25-30 (1998)

Miller et al. (Miller), "Targeted vectors for gene therapy," J. FASEB, Vol. 9, pp.190-199 (1995)

Claims 4 and 12 stand rejected under 35 U.S.C. § 112, first paragraph, as not enabled by the specification.

We reverse.

Background

The p53 gene encodes a tumor suppressor and the mutation of p53 is associated with cancer. Specification, page 6 ("[M]utational events associated with tumorigenesis occur in the p53 gene."). The specification discloses a

method of "supplying wild-type p53 function to a cell which carries mutant p53 alleles. The wild-type p53 gene or a part of the gene may be introduced into the cell in a vector such that the gene remains extrachromosomal. . . . If a gene portion is introduced and expressed in a cell carrying a mutant p53 allele, the gene portion should encode a part of the p53 protein which is required for non-neoplastic growth of the cell." Page 13. "More preferred is the situation where the wild-type p53 gene or a part of it is introduced into the mutant cell in such a way that it recombines with the endogenous mutant p53 gene present in the cell. Such recombination would require a double recombination event which would result in the correction of the p53 gene mutation. Vectors for introduction of genes both for recombination and for extrachromosomal maintenance are known in the art and any suitable vector may be used." Id.

Discussion

Claim 4 is directed to a method of supplying p53 function to a cell (which has lost p53 function) by introducing into the cell a portion of the human wild-type p53 gene, where the portion of p53 encoded by the gene is "required for non-neoplastic growth" of the cell. Claim 12 adds the limitation that the portion of p53 that is introduced includes the part of p53 that is mutated in the cell to be treated.

The examiner rejected all of the claims on the basis that undue experimentation would have been required to practice the claimed method. However, the examiner has acknowledged that a similar method using a full-length p53 gene is enabled. See the Examiner's Answer, pages 6-7. According to the examiner, a restriction requirement was made in a parent application and

the instant claims were held to be patentably distinct from claims to a method of supplying p53 function to cells using a full-length p53 gene. See the Examiner's Answer, page 6.

> Claims directed to the use of the full length p53 gene were elected for prosecution in the parent application. The parent application 08/035,366, is currently part of an interference before the board, Interference 104,066. . . . [T]he office acknowledges that methods of supplying a wild-type full length p53 gene to cells is [sic] enabled by the instant application. . . . However, the instant case is directed to patentably distinct methods of using portions of the p53 gene.

Specification, page 7 (emphasis in original).

Thus, the issue presented is whether, even though a method of supplying p53 function to a cell using a full-length p53 gene is enabled, it would have required undue experimentation to practice the same method using a part of the p53 gene that encode a functional portion of the p53 protein. The examiner concluded that

> in view of the art recognized unpredictability of determining from sequence data alone whether any "portion" of a gene would be able to fold correctly and exhibit wild type protein activity, the state of the art concerning p53 at the time of filing (i.e. 1992), the lack of guidance provided by the specification concerning the importance of amino acid residues outside of the 132-309 region which affect protein folding and/or p53 activity, the lack of guidance provided by the specification concerning the sequence or characteristics of any "portion" of p53 which is required for non-neoplastic growth, the lack of working examples either in vitro or in vivo which use a wild type p53 gene sequence which is a "portion" of the complete full length wild type sequence, the art recognized unpredictability of

> therapeutic gene delivery to target cell in vivo, and the breadth of the claims, it would have required undue experimentation to practice the invention as claimed.

Examiner's Answer, page 8.

Appellants argue that the references relied on by the examiner are not relevant to the instant claims, because they deal either with the effects of mutations on protein function, while the instant claims are limited to portions of the wild-type p53 sequence. See the Appeal Brief, pages 2-4. Appellants argue that the specification and prior art provide ample guidance to allow those skilled in the art to practice the claimed invention without undue experimentation. Appellants point to the specification's Figure 9, which shows that, of the 393 codons in the p53 gene, the bulk of mutations the inactivate p53 fall between codons 132 and 309. Appellants argue that these data would have led those skilled in the art to expect that at least the portion of p53 between codons 132 and 309 was "required for non-neoplastic growth," as recited in the claims.

Appellants also point to the prior art reference by Steinmeyer providing additional guidance. Appellants characterize Steinmeyer as disclosing that 40 amino acids at the N-terminus and an unspecified portion of the C-terminus of p53 were not required for DNA binding. Since "[b]inding to DNA is the mechanism by which wild-type p53 exerts its biological effect." Appellants assert that "by the priority date of the present application, those of skill in the art knew that portions of p53 were biologically active and would have understood that portions of p53 as recited in claims 4 and 12 need not contain C- or N-terminal amino acids to be functional." Appeal Brief, page 5.

The examiner bears the burden of showing a claimed invention is not enabled. See In re Wright, 999 F.2d 1557, 1561-62, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) ("When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application."). We agree with Appellants that the examiner has not carried that burden in this case.

The examiner has provided the starting point for our analysis, by conceding that the specification is adequate to enable claims to a method similar to that of the instant claims, but limited to using a full-length p53 gene. See the Examiner's Answer, page 7. The only additional experimentation required to practice the instant claims, relative to the concededly enabled claims, is determining the parts of the p53 gene that encode a portion of the p53 protein required for non-neoplastic cell growth. The only issue we must decide, therefore, is whether this additional experimentation would be undue.

We agree with Appellants that the specification would have led those skilled in the art to expect that the middle half of the p53 gene (encoding codons 132 to 309) was necessary for function, since mutations in that region resulted in non-functional variants of p53. See the specification, page 6, and Figure 9. We also agree with Appellants that Steinmeyer would have led those skilled in the art to expect that the N-terminal 40 amino acids and part of the C-terminus were not

needed for DNA binding, and therefore were not needed for p53 function. See Steinmeyer, page 504, right-hand column.

Taken together, then, the specification and Steinmeyer indicate that amino acids 132-309 are required for p53 function, and codons 1-40 and a certain number of codons at the N-terminus are not required. Thus, the experimentation required by the instant claims would appear to be limited to determining how many of the amino acids between positions 41 and 131, and how many of the codons between positions 310 and the C-terminal 393, could be deleted without adversely affecting the function of p53.

We agree with Appellants that this experimentation would not appear to be undue. At most, the skilled artisan would be required to make and test a series of deletion mutants of p53. This experimentation might be tedious, but it would not seem to be undue. See In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) ("[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.").

The examiner's evidentiary references do not appear to be on point. Bowie, Ngo, and Frommel all address the unpredictable effects that point mutations can have on the function of an encoded protein. Here, however, the

claims are limited to portions of the wild-type human p53 gene. Thus, the unpredictability evidenced by the references is not relevant to the claimed method. The examiner also cites several references as evidence that gene therapy was considered highly unpredictable as of the application's effective filing date. See the Examiner's Answer, pages 12-13. However, the examiner has conceded that the instant claims would be enabled if limited to the full-length p53 gene. The examiner has not explained why the asserted unpredictability of gene therapy raises an enablement problem for the instant claims but not for claims to the same method, carried out using a full-length p53 gene. In view of the Office's conclusion that claims limited to using a full-length p53 gene to supply p53 function are enabled by the instant specification, we do not find the examiner's concerns regarding gene therapy to be well-founded.

Summary

The examiner has not adequately shown that it would have required undue experimentation to determine which parts of the p53 gene encode portions of p53 required for non-neoplastic cell growth. Therefore, and since the examiner has conceded that the presently claimed method would be enabled if limited to the full-length p53 gene, we agree with Appellants that a prima facie

case of nonenablement has not been made. The rejection under 35 U.S.C. § 112, first paragraph, is reversed.

REVERSED

WILLIAM F. SMITH Administrative Patent Judge	)
DEMETRA J. MILLS Administrative Patent Judge	) BOARD OF PATENT) APPEALS AND) INTERFERENCES
ERIC GRIMES Administrative Patent Judge	)

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re:	Flannagan *et al.*	Confirmation No.:	5613
Appl. No.:	09/715,909	Group Art Unit:	1647
Filed:	November 17, 2000	Examiner:	Robert Hayes
For:	NOVEL BT TOXIN RECEPTORS FROM LEPIDOPTERAN INSECTS AND METHODS OF USE		

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RULE 132 DECLARATION
of
Cao Guo Yu

Sir:

I, Cao Guo Yu, do hereby declare and say as follows:

1. I am skilled in the art of the field of the invention. I earned the following academic degrees: a Master of Biochemistry at Fudan University in Shanghai, China (1982-1984), and a PhD of Microbiology at the University of Maryland, College Park, Maryland USA (1984-1990). As a post-doctoral fellow in the laboratory of Dr. Stephen Tobe of the Department of Zoology, University of Toronto, Canada, from 1990-1995, I identified and investigated expression of an allatostatin receptor using a mammalian cell system, established a cDNA library of brain, corpora allata and gut for studies of neurohormones and their receptors, developed a ligand binding assay and photoaffinity label assay for the characterization and purification of allatostatin receptors, determined functional groups of allatostatin using chemical modification and radiochemical assay, and investigated the mode of action of allatostatins and their receptors. From 1995-1999, I

worked for Norvartis Corporation, Research Triangle Park, North Carolina as a Staff Scientist. My major responsibilities were: identification and characterization of a receptor for VIP 3 using the yeast two hybrid system and biochemical methods, and the mode of action of VIP 3 and its receptor with cell culture system. From 1999 to date I have been working as a Research manager at Pioneer Hi-Bred International Inc., a DuPont company. My major responsibilities are: receptor identification and characterization of novel insecticidal toxins, studying the mode of action of novel toxins and their receptors, development of a high throughput system to identify novel genes with genomic and proteomic methodologies, and development of a bioassay for novel insecticidal toxins.

2. I have read and understand the above-referenced application.

3. The above-referenced application teaches that the toxin-binding site of the *ECB Bt* toxin receptor is found at about amino acids 4872-4928 of SEQ ID NO:2. Example 3 on pages 36-38 of this application provides an assay for determining the functionality of *ECB Bt* toxin. Based on the guidance provided in this application, I performed the following experiments to confirm that amino acids 4872-4928 of SEQ ID NO:2 were required for toxin binding activity. These experiments were performed essentially as described in Example 3 of the application. The experiments were conducted at Pioneer Hi-Bred

4. Bacmid expression constructs containing the full length or truncated *ECB Bt* toxin receptor coding sequences shown in Table 1 were prepared. These expression constructs were prepared using the pFastBac™ and pFastBac Dual™ expression vectors, which are available from Invitrogen™ (Carlsbad, CA).

Table 1

Construct Number	Description	Corresponding sequence
1	Full length *ECB Bt* toxin receptor	Amino acids 1-1717 of SEQ ID NO:2
3	Truncated *ECB Bt* toxin receptor with deleted transmembrane domain and cytoplasmic	Amino acids 1-1527 of SEQ ID NO:2

	domain	
5	Truncated *ECB Bt* toxin receptor containing only the transmembrane and cytoplasmic domain	Amino acids 1529-1717 of SEQ ID NO:2
7	*ECB Bt* toxin receptor with deleted cytoplasmic domain.	Amino Acids 1-1596 of SEQ ID NO:2
Control	Beta-glucuronidase (GUS)	

5. SF9 cells were transfected with the expression constructs listed in Table 1. Five days after transfection, the transfected cells were lysed and the expression of the receptor polypeptide was confirmed by Western blot analysis using a rabbit anti-BtR antibody.

6. The effects of the toxins Cry1F, Cry8, and Cry1A(b) on the full length *ECB Bt* toxin receptor were determined by applying each of these toxins to SF9 cells five days after transfection with Construct 1 from Table 1. Lysis of the transfected cells was observed in the presence of Cry1A at concentrations as low as 0.1 μg/ml. No cell lysis was observed in the presence of Cry1F or Cry8 toxin at concentrations up to 5 μg/ml.

7. The sensitivity of truncated *ECB Bt* toxin receptors to Cry1A(b) toxin was determined by applying the Cry1A(b) toxin at a concentration of 0.1 μg/ml to SF9 cells transfected with the *ECB Bt* toxin receptor expression constructs shown above in Table 1 and determining the level of toxin-mediated cell lysis. The results of this experiment are shown below in Table 2.

Table 2

Construct Number	**Description**	**Sensitive to Cry1A(b)?**
1	Full length *ECB Bt* toxin receptor	Yes
3	Truncated *ECB Bt* toxin receptor with deleted transmembrane domain and cytoplasmic domain	No
5	Truncated *ECB Bt* toxin receptor containing only the transmembrane and cytoplasmic domain	No
7	*ECB Bt* toxin receptor with deleted cytoplasmic domain.	Yes
Control	beta-glucuronidase (GUS)	No

The truncated receptor encoded by Construct 5, which did not contain the toxin binding site, did not show sensitivity to Cry1A(b). In contrast, the truncated receptor encoded by Construct 7, which contained a deletion in the cytoplasmic domain retained Cry1A(b) sensitivity.

8. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Cao Guo Xu

Nov. 8. 2004

Date